

REMARKS

The Office Action dated September 2, 2005 has been reviewed and the comments of the U.S. Patent and Trademark Office have been considered. The following remarks are respectfully submitted to place the application in condition for allowance. Claims 1, 3-19 and 21-22 are currently pending in this Application.

Rejections Under 35 U.S.C. §103(a)

Claims 1, 3-5 and 7-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Caskey et al (U.S. Patent No. 5,578,458) in view of Lee et al. (U.S. Patent No. 6,207,379) and Fauser et al (BioTechniques, 1997, 22(5):964-968). The Examiner states that Caskey discloses a method for identifying a SNP in an isothermal reaction. The Examiner further states that Lee teaches a method of diagnostic primer amplification utilizing an isothermal reaction and that it would have been obvious to apply the isothermal amplification of Lee to the amplification of Caskey. The Examiner concedes that Caskey does not teach the placement of the diagnostic nucleotides as taught in Applicants' claimed invention, but that this was known in the art as taught by Fauser. According to the Examiner, it would have been obvious to reposition the diagnostic nucleotide as taught by Caskey for the expected benefit of improved allele specificity as taught by Fauser. Applicants respectfully traverse this rejection.

In levying an obviousness rejection under 35 U.S.C. 103, the Examiner has the burden of establishing (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) that the prior art references, when combined, teach or suggest all the claim limitations. See MPEP §2143 (Aug. 2001, Latest Revision August 2005; *See also In re Royka*, 490 F.2d 981, 985 C.C.P.A. 1974). Here, the

Examiner has not met this burden. The present Office Action cited to Caskey at column 8, lines 7-30 for the teaching of an isothermal reaction. Applicants respectfully submit that the cited passage is being taken out of context. The cited passage describes *one step* in the amplification process described in Caskey, not the entire amplification process. The Examiner's attention is directed to Col. 7, L. 31-62, which describes the denaturation step. Here, the template solution is heated to 100°. Col. 7, L. 31-40. The specification states "Preferably, the temperature for the denaturation process ranges from about 90°C to 110°C, most preferably, the denaturation is carried out at about 105°C." Col. 7, L. 59-61. Caskey then describes the next step in the amplification process—hybridization or annealing of the primers to the template under competitive conditions. The temperature of the solution is lowered to between 10°C and 65°C, preferably 28°C. Col. 7, L. 3 to Col. 8, L. 6. The final step in Caskey's amplification process is that of the primer extension, described in the passage originally cited by the Examiner (Col. 8, L. 7-30). This passage describes only one part of the amplification process, that of primer extension. It is clear, after considering the above-cited portions of the patent (Col. 7, L. 3 – Col. 8, L. 30), that Caskey contemplates an amplification reaction which requires repeated temperature cycling to achieve denaturation, primer annealing and primer extension. This multi-temperature amplification is described in Example 1 ("The *heating, cooling* and DNA polymerization cycle were repeated approximately 10 times." Col. 13, L. 6-8, emphasis added). Examples 2 through 4 of the Caskey patent utilize these same heating/cooling steps for amplification. Therefore, Caskey neither teaches nor suggests an isothermal amplification reaction.

The cited secondary references do not cure the deficiencies of Caskey. Lee primarily describes the use of a non-conventional primer in a non-isothermal PCR reaction. The primers

are used for the detection and amplification of target nucleic acid sequences where the specificity is increased such that at least one primer is capable of recognizing two or more regions on the template. Col. 2, L. 12. Although Lee mentions in passing that “linear amplification may be affected at melting temperature” (as cited by the Examiner at Col. 7, L. 53-60), the mere existence of an isothermal amplification reaction at the time of the invention does not suggest the current claims. Nowhere does Lee contemplate or teach the detection of a single nucleotide polymorphism. Further Fauser utilizes a non-isothermal (PCR) amplification reaction. Page 965, Col. 2-3. Therefore, the combination of the cited references do not teach or suggest all of the present claim limitations, specifically, the use of an isothermal amplification reaction. In addition, there is no suggestion or motivation in the reference, or within the knowledge of one of ordinary skill in the art, to alter the secondary reference to arrive at the current claim because none of the references contemplate this isothermal amplification reaction.

The Examiner must also show that there is a reasonable expectation of success in altering the cited references, and that the expectation of success is found in the reference. See *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the Examiner is using impermissible hindsight in reaching the conclusion that there was a reasonable expectation of success. Although “the instant claims are drawn to isothermal amplification, not PCR” (as argued by the Examiner in the Office Action dated 9/2/05), the art at the time of the invention indicated to the person of ordinary skill that the primers of the current claims did not work in a non-isothermal PCR reaction. Applicants previously argued that the cited prior art (Kwok et al., 1990, *Nucleic Acids Research* 18:999-1005) teaches away from the claimed invention and, therefore, there was no reasonable expectation of success. In particular, Kwok states in his abstract:

“We investigated the effects of various primer-template mismatches on DNA amplification of an HIV-1 *gag* region by the polymerase chain reaction (PCR). **Single internal mismatches had no significant effect on PCR product yield** [i.e., primer extension occurs normally] while those at the 3’ terminal base had varied effects.” (emphasis added)

Kwok further states on page 1003, first column:

“In the process of generating templates with altered bases, we demonstrated that a single mismatch 3 residues from the 3’ terminal base of a primer can be efficiently extended without modification of amplification reaction conditions. **Similarly, mismatches 1, 2, or 3 bases from the 3’ nucleotide of primer had no apparent affect on overall PCR product yield.**[i.e., primer extension occurs normally]” (emphasis added)

Therefore, that same person of ordinary skill had no reasonable expectation that the primers of the current claims would work in the isothermal amplification reaction of the current claims. Stated another way, the prior art taught away from the current claims. Applicants respectfully request withdrawal of the rejection.

Claims 6 and 18-22 are rejected under 35 U.S.C. §103(a) as being unpatentable over Caskey et al. in view of Fauser et al. as applied to claim 1 above and further in view of Whitcomb et al. (U.S. Patent 6,326,145). The Examiner characterized Caskey as outlined above. The Examiner concedes that Caskey does not teach tailed primers of Applicants’ invention but that these elements were well known in the art as taught by Whitcomb.

Applicants respectfully traverse this rejection. For the reasons outlined above, the combination of Caskey and Lee does not result in Applicant’s currently claimed invention of an isothermal amplification reaction. Whitcomb does not cure this deficiency. Whitcomb describes a method of detecting a target nucleic acid utilizing a non-isothermal amplification reaction. PCR amplification is described throughout the application, and all of the Examples use temperature cycling as the means of amplification. Although Whitcomb mentions strand displacement amplification (as cited by the Examiner), the mere existence of an isothermal

amplification reaction at the time of the invention does not suggest the current claims. Whitcomb never contemplates nor teaches detection of single nucleotide polymorphisms. The combination of the prior art cited by the Examiner therefore does not teach Applicants' currently claimed invention. Withdrawal of the rejection is respectfully requested.

Claim Rejection-Double Patenting

Claims 1, 3-19 and 21-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 13, 14, 16, 17 and 19-23 of copending application Serial No. 10/202,896.

Applicants respectfully request the rejection be held in abeyance pending indication of allowable subject matter.

CONCLUSION

Applicant respectfully submits that the claims now stand ready and in condition for allowance.

A request for Extension of Time under the provisions of 37 CFR §1.136(b) and the appropriate fee are submitted concurrently with this amendment. The U.S. Patent and Trademark Office is hereby authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 020187.0100.

Early and favorable action on the merits is respectfully requested. The Examiner is invited to contact the undersigned if necessary to expedite the prosecution of the instant application.

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